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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,230	VAN DEN BRINK ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 25-33* is/are pending in the application.

4a) Of the above claim(s) *25-29,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,30 and 31* is/are rejected.

7)☒ Claim(s) *5,12 and 13* is/are objected to.

8)☒ Claim(s) *1-13 and 25-33* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 8/27/07 has been entered in full. Claims 4 and 30 are amended (claims 14-24 were previously canceled by Applicants).

Claims 1-3 and 25-33 are pending in the instant application.

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-13, 30 and 31, in the reply filed on 8/27/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 25-29, 32 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/27/07.

Two elections of species were required.

Applicants' election of the species of (1) nucleic acid expression vector and (2) colon (large intestinal) cancer in the reply filed on 8/27/07 is acknowledged.

However, on further consideration by the Examiner, the requirement for each election of species is withdrawn.

Claims 1-13, 30 and 31 are under consideration.

Specification

The disclosure is objected to because of the following informalities:

(1) A priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the priority statement should indicate that the instant application is a 371 of PCT/NL03/00127 filed 2/20/03.

(2) The disclosure is objected to because it contains an embedded hyperlink at page 15, line 32. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01 (part VII).

Appropriate correction is required.

Claim Objections

Claims 5, 12 and 13 are objected to because of the following informalities:

(1) There is an extraneous space between the final word of claim 5 and the period (i.e., the claim ends with "...carcinoma ." This space should be deleted.

(2) Claims 12 and 13 each contain an extraneous space after the number "30" in the recitation of "...according to claim 30 , wherein..." This space should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of treating a deficiency of a hedgehog protein in the gastrointestinal (GI) tract comprising administering a composition that comprises a source of a Hedgehog protein.

The specification provides two working examples related to the claimed invention (pg 34-40), directed to "colonic tissues" (Example 1) and "gastric tissues" (Example 2). Example 1.1 describes expression of Sonic and Indian hedgehog (Shh and Ihh) mRNA and protein in the colon, reporting that "only Ihh protein is detectable in the adult colon". Example 1.3 teaches that "Ihh staining was completely lost" in "adenomatous polyps" and "was lost in 8 out 9 carcinomas" and "loss of Ihh expression already occurs at the polyp stage" (pg 36). Example 1.4 teaches that either butyrate or recombinant Shh protein (which "has a higher biological activity than recombinant Ihh") can induce Villin expression in the colon cancer cell line HT-29, which is a marker indicating that differentiation has been restored. Example 1.5 teaches that butyrate induction of HT-29 can be blocked with the hedgehog pathway inhibitor cyclopamine. Example 2.1 describes teaches that in "the length of the human GI tract" Shh protein is found only in the "fundic glands of the stomach" (pg 38). Example 2.2 demonstrates that Shh protein expression is lost in areas of intestinal metaplasia ("replacement of gastric epithelium by epithelium of intestinal phenotype" and a "risk factor for development of gastric adenocarcinoma") (pg 38). Example 2.3 teaches that "aberrant development of intestinal epithelium into gastric epithelium with fundic glands is accompanied by Shh expression". Example 2.4 teaches that in patients with Barrett's esophagus "the switch in differentiation from squamous [epithelium of the esophagous] to gastric epithelial tissue with fundic glands is accompanied by induction of Shh expression". It is noted that Examples 2.3 and 2.4 deal with aberrant Hedgehog protein expression, rather than a deficiency of Hedgehog protein in the GI tract, and therefore do not relate to the claimed invention. None of the working examples demonstrate treatment of a deficiency in a Hedgehog protein in a subject.

The relevant art teaches that the role of hedgehog proteins in the adult human gastrointestinal tract is complex and not well understood. For example, van den Brink (2007. Physiol Rev. 87(4):1343-75) teaches that while Indian hedgehog "expression is

lost very early in the process of colorectal carcinogenesis in humans" (pg 1368) "the relevance of the loss of Hedgehog signaling in colorectal carcinogenesis is not yet clear" (pg 1369). van den Brink teaches that it remains possible that the loss of Hedgehog signaling in the early stages of distal colon carcinogenesis is "an epiphenomenon" rather than playing "a causal role" (pg 1370). van den Brink reports that different studies have provided conflicting results as to whether or not hedgehog signaling is active in colorectal cancer cells (pg 1368-1369) and that "at later stages of carcinogenesis there is a gain of Hedgehog signaling that maintains viability of carcinoma cells" (pg 1370). van den Brink also teaches, "[t]he spectacular effect of SMO inhibition on the viability of many gastrointestinal cancer cell lines suggests that the Hedgehog pathway may be an attractive target for cancer therapy" (pg 1369). Furthermore, while Applicants report that butyrate induces expression of Indian hedgehog in colon cancer cells, the relevant art reports that the ability of butyrate administration to treat colon cancer is controversial. Lupton (2004) teaches that "[b]utyrate, an SCFA (small chain fatty acid) fiber fermentation product, is thought to be chemopreventative by some, but not all studies show this beneficial effect against colon cancer development" (pg 479 of Lupton et al. 2004. Journal of Nutrition. 134(2): 479-482). Lupton also teaches that one study found that administration of butyrate "actually increased the percentage of rats with tumors" (pg 480). Furthermore, Tonelli et al (1995) reports that in "FAP [familial adenomatous polyposis] patients SCFA [including butyrate] did not alter proliferation ... FAP patients are refractory to SCFA" (see Abstract of Tonelli et al. 1995. Dis Colon Rectum. 38(9): 974-978). In view of the teachings of the specification and the relevant art, the skilled artisan could not predict whether administration of a Hedgehog protein (e.g., Indian) to a subject with a deficiency in a Hedgehog protein (e.g., lack of Indian in a colon cancer) would treat the deficiency, have no effect, or instead stimulate the hedgehog pathway further, resulting in cancerous growth. It would require undue experimentation to test subjects with such deficiencies to determine whether or not such treatment would effective.

Furthermore, the scope of the claims is significant with respect to the deficiency to be treated, the nature of the treatment and the source of the administered Hedgehog

protein. The broadest claims are directed to a deficiency of any Hedgehog protein (e.g., Sonic, Desert, Indian or variants thereof) in any portion of the GI tract (which broadly encompasses the oral cavity, tongue, salivary glands, pharynx, esophagus, stomach, colon, cecum, appendix, ileum (small intestine), rectum and anus, as well as associated organs including the liver, gallbladder and pancreas). Specifically recited embodiments include gastric cancer including carcinomas, colon cancer including carcinomas, familial adenomatous polyposis coli (FAP), colonic adenomatous polyps, invasive adenocarcinomas, small intestinal adenomas and cancers and desmoid tumors. Furthermore, the claims encompass treatment of either adult or developing (e.g., embryonic) subjects with a GI tract hedgehog deficiency. In contrast to this breadth of the claims, the specification only provides two examples of a Hedgehog protein deficiency in the GI tract: loss of Ihh in the colon (adenomatous polyps and adenocarcinomas) and loss of Shh in intestinal metaplasia of the fundus. These two limited examples are not sufficient to provide enablement for the full range of potential GI tract ailments that are encompassed by the claims. In fact, the specification teaches that Shh is expressed in fundic gland heterotopia of the small intestine and fundic gland metaplasia of the esophagus. This demonstrates that lack of Shh expression is not common to all ailments of the GI tract. It would require undue experimentation to test all of the possible ailments of the GI tract to determine which if any are associated with a Hedgehog deficiency. It is noted that the claims 3 and 5 recite the species of "gastric cancer", yet no evidence exists of Hedgehog protein loss in gastric cancer (intestinal metaplasia of the fundus is not a form of gastric cancer). However, van den Brink (2007) reports that "cancer cell lines derived from the esophagus, stomach, pancreas and biliary tract showed high autonomous Hedgehog pathway activity. This was supported by the demonstration that PCT1 mRNA expression was highly induced in gastric and pancreatic carcinomas compared with adjacent normal tissue" (pg 1367-1368).

Furthermore, the term "treating" as used in the claims encompasses not only therapy of patients suffering from a Hedgehog deficiency (e.g. patients with cancer resulting from said deficiency) but also prevention of said diseases occurring in "at risk" patients. As such, the claims require the skilled artisan to be able to diagnosis "at risk"

patients, and prevent occurrence of disease therein. However, in view of the lack of enablement for methods of therapy of diseases (e.g., cancer) as described above, the claims also lack enablement for prevention of said diseases.

Furthermore, the claims encompass methods of treatment comprising administration of compositions comprising a genus of variant sources of a Hedgehog protein. These sources include "a Hedgehog protein or an active homologue or variant thereof"; nucleic acid vectors, enteric bacteria and animal cells encoding said proteins; and "a molecule or agent that induces or upregulates expression of Hedgehog protein". Claims 1-7 are generic to said genus of sources. Claims 7, 8, 9, 30 and 31 are directed to methods that encompass each type of source as a Markush-type group. Claims 10, 11, 12 and 13 each limit the source to one particular subgenus, i.e., variant Hedgehog polypeptides (claims 10 and 11), nucleic acid vectors encoding variant Hedgehog polypeptides (claim 12) and enteric bacterium encoding variant Hedgehog polypeptides (claim 13). The claims do not place any limitation on the amount of variation permitted in Hedgehog homologues or variants, except that claim 30 recites "active homologue or variant". Is noted that it is not clear whether or not the term "active" applies to both homologue and variant in claim 30 (see "Claim Rejections under 35 USC 112, 2nd paragraph"). The specification teaches that "[t]he term "Hedgehog" as used herein thus comprises polypeptides preferably having at least 63% amino acid identity with the amino acid sequence of SEQ ID NO: 1 [human Desert hedgehog], SEQ ID NO: 2 [human Indian hedgehog], SEQ ID NO: 3 [human Sonic hedgehog]..." (pg 4, line lines 19-21). The use of the term "preferably" indicates that encompassed variants are not limited to those with at least 63% identity. As such, the claims encompass method of using a genus of variant Hedgehog polypeptides (and related nucleic acids and cells) that is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the variant polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims only require the claimed polypeptides share some structural similarity to the isolated polypeptide of SEQ ID NO: 1, 2, or 3. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. None of the

claims include the limitation that the polypeptide variants exhibit characteristics of the parent polypeptide of SEQ ID NO: 1, 2 or 3. Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 1, 2 or 3 and variants thereof. If a variant of the protein is to have a structure and function similar to the protein corresponding to SEQ ID NO: 1, 2 or 3, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein. Conversely, if a protein variant of SEQ ID NO: 1, 2 or 3 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, claims 1-9, 11-13, 30 and 31 each encompass treatment by administration of a nucleic acid that encodes a Hedgehog protein or homologue or variant thereof. However, the specification does not teach any methods or working

examples that indicate the claimed nucleic acid is introduced to an organism by administration and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, the claims encompass treatment with a genus of molecules or agents that induce or upregulate expression of Hedgehog protein in a subject. Such molecules and agents lack enablement for methods of treatment for the same reason as for administration of Hedgehog protein set forth above. Furthermore, the only example of such a compound in the specification is butyrate, which is used in Example 1.4 to induce Indian hedgehog expression in the colon cancer cell line HT-29. However, the term "agent or molecule" as used in the claim is not limited by any structure, and this recitation potentially encompasses any sort of protein, nucleic acid, lipid, carbohydrate, small organic molecule, large organic molecule and more. It would require undue experimentation to make and test the large genus of potential molecules and agents in order to determine which have the ability to induce Hedgehog expression, and then to determine which could be used for treatment.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-13, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are genus claims encompassing methods of treatment comprising administration of compositions comprising a genus of variant sources of a Hedgehog protein. These sources include "a Hedgehog protein or an active homologue or variant thereof"; nucleic acid vectors, enteric bacteria and animal cells encoding said proteins; and "a molecule or agent that induces or upregulates expression of Hedgehog protein". Claims 1-7 are generic to said genus of sources. Claims 7, 8, 9, 30 and 31 are directed to methods that encompass each type of source as a Markush-type group. Claims 10, 11, 12 and 13 each limit the source to one particular subgenus, i.e., variant Hedgehog

polypeptides (claims 10 and 11), nucleic acid vectors encoding variant Hedgehog polypeptides (claim 12) and enteric bacterium encoding variant Hedgehog polypeptides (claim 13). The claims do not place any limitation on the amount of variation permitted in Hedgehog homologues or variants, except that claim 30 recites "active homologue or variant". Is noted that it is not clear whether or not the term "active" applies to both homologue and variant in claim 30 (see "Claim Rejections under 35 USC 112, 2nd paragraph"). The specification teaches that "[t]he term "Hedgehog" as used herein thus comprises polypeptides preferably having at least 63% amino acid identity with the amino acid sequence of SEQ ID NO: 1 [human Desert hedgehog], SEQ ID NO: 2 [human Indian hedgehog], SEQ ID NO: 3 [human Sonic hedgehog]..." (pg 4, line lines 19-21). The use of the term "preferably" indicates that encompassed variants are not limited to those with at least 63% identity. As such, the claims encompass method of using a genus of variant Hedgehog polypeptides (and related nucleic acids and cells) that is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the variant polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims only require the claimed polypeptides share some structural similarity to the isolated polypeptide of SEQ ID NO: 1, 2, or 3. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity.

With respect to the genus of "a molecule or agent that induces or upregulates expression of Hedgehog protein", the only example of such a compound in the specification is butyrate, which is used in Example 1.4 to induce Indian hedgehog expression in the colon cancer cell line HT-29. However, the term "agent or molecule" as used in the claim is not limited by any structure, and this recitation potentially encompasses any sort of protein, nucleic acid, lipid, carbohydrate, small organic molecule, large organic molecule and more.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics

coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides, nucleic acids, cells, molecules or agents. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred,

regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of treating a deficiency of a Hedgehog protein in the GI tract of a subject deficient in said protein and in need of such treatment, comprising administration of the polypeptides of SEQ ID NO: 1, 2 or 3, or the molecule butyrate, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "deficient" in claim 1 is a relative term which renders the claim indefinite. The term "deficient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, Sonic hedgehog protein is undetectable in adult human colon, but is detectable in adult human stomach (see page 34, lines 1-14). It is unclear whether or not this is considered a deficiency in a Hedgehog protein.

Claim 1 is also indefinite in that it recites the acronym "GI". Use of acronyms results in indefinite language. Therefore, when used for the first time scientific terms should be completely spelled out.

Claim 30 is indefinite because it is not clear in the recitation "active homologue or variant" whether or not the term "active" applies to "homologue" alone or both "homologue" and "variant".

Claim 31 is indefinite in that it recites the acronyms "Shh" and "Ihh". Use of acronyms results in indefinite language. Therefore, when used for the first time scientific terms should be completely spelled out.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-9, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Tonelli et al, 1995 (Dis Colon Rectum. 38(9): 974-978).

The recitation of "treating a deficiency of a Hedgehog protein in the GI tract of a subject deficient in said protein" in the preamble of claim 1 from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art, except in so far as it limits to the claimed method to one wherein the subject has a deficiency of a Hedgehog protein.

Furthermore, the instant specification and relevant art teach that patients with familial adenomatous polyposis (FAP) inherently have a deficiency of Indian hedgehog in adenomatous polyps (pg 36, line 14-15 and pg 279-280 of van den Brink et al, 2004. Nature Genetics. 36(3): 277-282; cited herein only to support inherency). Therefore, a subject with FAP meets the limitation of claim 1 that the

subject has a deficiency of a Hedgehog protein. Furthermore, the "source of a Hedgehog protein" recited in claim 1 encompasses "a molecule or agent that induces or upregulates expression of Hedgehog protein in said subject". The instant specification and relevant art teach that the compound butyrate inherently upregulates expression of Indian hedgehog (pg 37, line 19-20 and pg 277 of van den Brink et al, 2004; cited above). Therefore, the method of claim 1 encompasses a method of administration of butyrate to a subject with FAP. Tonelli teaches such a method (see Abstract); as such, Tonelli anticipates claim 1.

Each of claims 6-9, 30 and 31 encompasses the same method described with respect to claim 1; therefore Tonelli also anticipates each of these claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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